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Limited Assessment of Respiratory Muscle Response to Nusinersen Treatment in Infants with Spinal Muscular Atrophy

To the Editor:

Optoelectric plethysmography is a novel and interesting method of assessing breathing patterns and thoracoabdominal paradox in children with spinal muscular atrophy (SMA). LoMauro and colleagues should be commended for their efforts to quantify breathing parameters in this group of children (1). Respiratory assessment of infants with SMA is important and necessary to better understand the effects of treatments on respiratory muscle strength and respiratory function (2).

Although LoMauro and colleagues did show a reduction in thoracoabdominal paradox in patients with SMA type 1C treated with nusinersen compared with untreated patients with type 1C, the patient groups they compared may not be equivalent. The treated group had higher SMN (survival motor neuron) copy numbers, which is associated with better outcomes and a milder clinical course. Patients in the treated group were significantly older than those in the untreated group, with treated patients with type 1C being the oldest of all. It is difficult to distinguish the effects of disease treatment from those of growth and development in the absence of appropriate reference data, especially considering that chest wall compliance and thoracoabdominal paradox decrease with age. Despite these differences between the patient groups, there is little doubt about the potential value of optoelectric plethysmography for providing objective outcome measures in clinical or epidemiological research studies involving infants with SMA. However, it is generally agreed that no single lung function test will ever provide the answer and that a combination of tests is required. Other respiratory assessment tools are available for children in this age group, including the widely available thoracic and abdominal effort respiratory impedance plethysmography bands, which are frequently incorporated into polysomnography recordings and record respiratory rate and thoracoabdominal paradox. It would be very interesting to compare these two methods of assessment in young children with SMA for use as clinical trial outcomes. In addition, oscillometry in children with SMA has been shown to provide valuable information and may be useful for assessing response to therapeutic interventions such as disease-modifying agents, including nusinersen (3).

One of the dangers of publishing incomplete data on respiratory outcomes in young patients with SMA is the potential risk that medical insurance companies or funding bodies will use these data to deny reimbursement for or access to treatment with a potentially life-saving medication. Thus, although LoMauro and colleagues have added valuable information regarding the respiratory effects of nusinersen in infants with SMA, we caution against concluding that types 1A and 1B did not show a treatment response based on optoelectric plethysmography alone. Major gaps in our knowledge and understanding of treatment response in SMA remain. ■

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Reply to Chacko *et al.*

From the Authors:

We thank Chacko and colleagues for their interest in our study (1). We agree that multiple factors must be considered when discussing

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access and reimbursement criteria, and that a combination of tests is advisable to assess the therapeutic effects of drugs. In fact, we also reported Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (2, 3) scores and daily hours of mechanical ventilation (1).

In our study, motor function, ventilatory support, respiratory rate, and V_T improved in patients with spinal muscular atrophy (SMA) treated with nusinersen compared with untreated patients irrespective of disease severity, with those with type 1C showing the highest values. Inspiratory paradox of the rib cage (IPRC) was present in treated patients with SMA1 A and B but not in those with type 1C.

Optoelectronic plethysmography (OEP) allows one to gather additional information about the pathophysiology of SMA in a noninvasive manner by providing nonvolitional global and specific indexes of respiratory function. We think that the alternative tools proposed by Chacko and colleagues—respiratory impedance plethysmography (RIP) (4) and forced oscillation technique (FOT) (5)—may have some limitations and may not provide additional information about the effect of nusinersen on respiratory function.

RIP provides qualitative information regarding thoracoabdominal asynchronies by measuring changes in only two cross-sectional areas. Its limited calibration methods to estimate chest wall/lung volume require subject-specific calibration during a long period of regular breathing, which can be problematic in infants and children because they frequently may cry, babble, or speak.

Conversely, OEP provides accurate chest wall volumes and anatomical thoracoabdominal subdivision, and its calibration does not depend on the subject. We agree, however, that studies comparing the two techniques would be of interest, because RIP is more widely available.

FOT has great clinical potential, but it provides data on passive properties (resistance and reactance) of the respiratory system rather than on the force/action of respiratory muscles. FOT does not discriminate between obstructive and restrictive lung disorders (5) and was shown by Gauld and colleagues to not differentiate between SMA2 and SMA3 (6), while OEP data were sensitive to disease severity (7). FOT still needs to be extensively investigated in SMA1 (8), and no reliable reference values are available for young children (6).

Our data provide further insights into the mechanisms underlying different individual responses to treatment, but they cannot be interpreted as supporting access to or exclusion from treatment or as parameters for starting or stopping treatment, as several other factors must be considered. We showed that IPRC was still present in our treated children with SMA1 A and B (1), but IPRC *per se* is not a problem, as it is present in healthy infants (9). When IPRC is accompanied by breathing difficulties, it becomes a medical emergency. In SMA, it is the consequence of progressive ribcage muscle weakness/atrophy that triggers a cascade of events: inefficient cough (coughing relies principally on ribcage muscles [10]), bell-shaped chest (11), hypoventilation, atelectasis (associated with recurrent aspiration due to bulbar impairment), excessive work of breathing, and ventilatory failure.

Future larger studies are needed to identify drug responders and nonresponders, with age of symptoms onset, clinical presentation (including IPRC), and SMN2 copy numbers as independent factors.

Of note, SMN2 copy numbers did not affect our results, as they were equally distributed (50% with two copies and 50% with three copies) with no difference between the two groups.

We do not think that age may have played a role in our results, because *1*) clinical evidence suggests that IPRC gets worse with age in natural-history SMA1 owing to the progression of weakness/atrophy of the ribcage muscles (12, 13), *2*) the two treated groups were similar in age (21 mo [1A and 1B] and 29.7 mo [1C]) (1), and *3*) physiological IPRC should not be present in the awake state at those ages.

In conclusion, we believe that our study provides important data for future studies seeking to better understand the effects of nusinersen and other emerging drugs on respiratory function in patients with SMA. ■

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On the 2019 Spirometry Statement

To the Editor:

The awaited Standardization of Spirometry 2019 Update (1) sheds light on many aspects not entirely covered in the previous 2005 edition (2). As with the former edition, it is called to be the most referenced source for the practice of this widely used device, but some issues are still not covered.

Once more, the importance of daily calibration or verification is stressed, even though some manufacturers state that their devices do not require such controls at all. A pitfall to its fulfillment is that calibration syringes are sold as a separate accessory, so the customers do not feel they are a must. Future versions of this statement should address this subject, urging manufacturers to include syringes as part of the spirometer. Furthermore, effective quality control is a problem in some scenarios, such as inpatient facilities. Ambient conditions are often different from those in which the equipment is stored and calibrated, such as the pulmonary function laboratory. Ideally, a calibration syringe should be transported to that facility, but this is seldom done because of practical reasons. At the very least, room temperature should be checked and updated in the spirometer before testing.

Patient identification has important legal significance. In many countries, women use their husband's last names. But when they separate or divorce, their last name changes and another identification may be created, which means that trend reports and graphics cannot be accurately assembled. To avoid this, every person should be identified by their original name as it appears in their identity documents. This recommendation could also apply to public people using surnames, such as actors and politicians.

Some defects overestimate FVC or FEV_1. For example, in a maneuver with a reinhalation defect, FVC is overestimated, but FEV_1 is still valid. If rejected, a significant FEV_1 value could be missed. If not, it will be probably be ranked as the best, based on the highest sum of FVC and FEV_1, and be displayed in the final report. The software should incorporate the capacity of accepting or rejecting individual FVC and FEV_1 values coming from unacceptable maneuvers.

The statement mentions that if FEV_1 falls below 80% of the start value, the test should be terminated, but this is sometimes hard for the operator to detect, as many software programs list maneuvers according to the sum of FVC and FEV_1. This task would be easier if the maneuvers were custom sorted.

Operators must seek to obtain maneuvers of similar expiratory time before and after bronchodilator administration, and software should allow isotime readings (e.g., FEV_4 to FEV_{15}), to overcome the problem of overestimated response when forced expiratory time is significantly longer in post- than in prebronchodilator maneuvers. Another alternative is the implementation of sliding vertical bars across the volume/time graph that the operator can use to equate forced expiratory time between pre- and post-bronchodilator sets. Another issue of importance concerning bronchodilator response is that it may be present even in the absence of numerical criteria. Patients in whom cough disappears or who refer a change in the quality of their respiration after bronchodilator administration are worth a comment by the operator.

Finally, spirometry in the supine position has become a standard practice in the evaluation of patients with orthopnea, or suspected or definite neuromuscular disorders (3). A future section on the subject is desirable, along with recommendations for manufacturers to add a phase other than pre- and post-bronchodilator for better comparison between sitting and supine positions and differential indexing in databases.

Expert and evidence-based American Thoracic Society/European Respiratory Society statements have had a great effect on the unification of practice and clinical trial methodology. Most spirometry training courses worldwide are and will be based on them (4, 5). We are living in a time in which new evidence and technologies are helping to further improve this old practice, and respiratory societies are keeping the pace. ■

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